

ORIGINAL ARTICLE

Glycopyrronium tosylate in pediatric primary axillary hyperhidrosis: Post hoc analysis of efficacy and safety findings by age from two phase three randomized controlled trials

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Abstract

Objectives: Hyperhidrosis in pediatric patients has been understudied. Post hoc analyses of two phase 3 randomized, vehicle-controlled, 4-week trials (ATMOS-1 [NCT02530281] and ATMOS-2 [NCT02530294]) were performed to assess efficacy and safety of topical anticholinergic glycopyrronium tosylate (GT) in pediatric patients.

Methods: Patients had primary axillary hyperhidrosis ≥ 6 months, average Axillary Sweating Daily Diary (ASDD/ASDD-Children [ASDD-C]) Item 2 (sweating severity) score ≥ 4 , sweat production ≥ 50 mg/5 min (each axilla), and Hyperhidrosis Disease Severity Scale (HDSS) ≥ 3 . Coprimary end points were ≥ 4 -point improvement on ASDD/ASDD-C Item 2 (a validated patient-reported outcome) and change in gravimetrically measured sweat production at Week 4. Efficacy and safety data are shown through Week 4 for the pediatric (≥ 9 to ≤ 16 years) vs older (> 16 years) subgroups.

Results: Six hundred and ninety-seven patients were randomized in ATMOS-1/ATMOS-2 (GT, N = 463; vehicle, N = 234); 44 were ≥ 9 to ≤ 16 years (GT, n = 25; vehicle, n = 19). Baseline disease characteristics were generally similar across subgroups. GT-treated pediatric vs older patients had comparable improvements in ASDD/ASDD-C Item 2 (sweating severity) responder rate, HDSS responder rate (≥ 2 -grade improvement), sweat production, and quality of life (mean change from Baseline in Dermatology Life Quality Index [DLQI]/children's DLQI), with greater improvement vs vehicle. Treatment-emergent adverse events were similar between subgroups, and most were mild, transient, and infrequently led to discontinuation.

Conclusions: Topical, once-daily GT improved disease severity (ASDD/ASDD-C, HDSS), sweat production, and quality of life (DLQI), with similar findings in children, adults, and the pooled population. GT was well tolerated, and treatment-emergent adverse events were qualitatively similar between subgroups and consistent with other anticholinergics.

1 | INTRODUCTION

Hyperhidrosis is characterized by excess sweat production beyond what is necessary to maintain thermal homeostasis. In primary hyperhidrosis, idiopathic sympathetic nerve hyperactivity triggers excess sweating, most commonly of the axillae, palms, soles, or craniofacial regions.¹ Hyperhidrosis occurs in children and adults, with ~4.8% of the US population (~15.3 million people) affected.^{1,2} In an online survey of US teens, ~17.1% experienced excessive sweating, with a mean onset age of 11 years.³ The substantial negative impact of hyperhidrosis on quality of life has been well established⁴⁻⁷ and equated as comparable to, or greater than, the impact of psoriasis or eczema.⁸ In children, the condition negatively affects psychological and social development and well-being, which may consequently trigger emotional and social distress.⁹

Hyperhidrosis largely remains underrecognized as a treatable medical condition, particularly for pediatric patients.^{6,10} Only 51% of patients discussed their excess sweating with a health care professional, possibly due to patients' inability to recognize symptoms as a medical condition and/or dissatisfaction with available therapies.^{1,11} Though not pediatric-specific, these findings highlight the need for increased awareness and new treatments.⁶ Glycopyrronium tosylate (GT; formerly DRM04) is a topical anticholinergic approved by the US Food and Drug Administration (June 2018) for primary axillary hyperhidrosis in patients 9 years and older (QBREXZA™ [glycopyrronium] cloth, 2.4%, for topical use). GT is applied once-daily to the axillae using a premoistened towelette. GT-treated patients had decreased sweating severity and sweat production, with improvements in quality of life vs vehicle-treated patients in two randomized, double-blind vehicle-controlled, pivotal phase three studies for primary axillary hyperhidrosis (ATMOS-1, N = 344 [NCT02530281] and ATMOS-2, N = 353 [NCT02530294]).¹² ATMOS-1 and ATMOS-2 were the first randomized, controlled phase three trials in primary axillary hyperhidrosis to enroll pediatric patients, offering a unique perspective into this underserved population. To better characterize treatment outcomes in pediatric patients, pooled efficacy and safety data for pediatric (≥ 9 to ≤ 16 years) vs older patients (> 16 years) were evaluated in a post hoc analysis of ATMOS-1 and ATMOS-2.

2 | MATERIALS AND METHODS

2.1 | Study design

ATMOS-1 (US and Germany sites) and ATMOS-2 (US sites only) assessed the efficacy and safety of GT vs vehicle when applied once-daily for 4 weeks (Figure 1). A detailed description of trial methodology and approval by local institutional review boards have been reported.¹² Patients were assessed in clinics at Weeks 1, 2, 3, and 4 (end of treatment).

2.2 | Study patients

Detailed inclusion and exclusion criteria are fully reported in the primary publication.¹² Briefly, patients were male or nonpregnant

females ≥ 9 years of age (≥ 18 years in Germany) with primary axillary hyperhidrosis for ≥ 6 months, gravimetrically measured sweat production ≥ 50 mg/5 min in each axilla, Axillary Sweating Daily Diary (ASDD)/ASDD-Children (ASDD-C) axillary sweating severity item (Item 2) ≥ 4 (11-point scale),^{13,14} and Hyperhidrosis Disease Severity Scale (HDSS) ≥ 3 (4-point scale).

2.3 | Efficacy and safety assessments

In ATMOS-1 and ATMOS-2, coprimary efficacy end points were ASDD/ASDD-C Item 2 (sweating severity) responder rate (≥ 4 -point improvement from Baseline) and mean absolute change from Baseline in gravimetrically measured sweat production (average of left and right axillae) at Week 4.¹² Whereas the adult ASDD assesses severity (Item 2), impact (Item 3), and bothersomeness (Item 4) of axillary sweating, the children's version only assesses severity (Item 2) and was completed by patients ≥ 9 to < 16 years. Item 2 was specifically developed and rigorously validated in accordance with FDA patient-reported outcome (PRO) guidance¹⁵ to support efficacy assessments for regulatory approval. A 4-point improvement was identified as the threshold for meaningful clinical response.¹⁴ Gravimetrically measured sweat production was assessed once a week over a 5-minute period under controlled conditions across study sites.

ATMOS-1 and ATMOS-2 also assessed two additional PRO measures, namely the HDSS and Dermatology Life Quality Index (DLQI; patients > 16 years) and children's version (CDLQI; patients ≤ 16 years). The HDSS, a validated hyperhidrosis-specific PRO measure for assessing sweating severity, is a self-reported questionnaire that employs a scale from 1 (never noticeable/never interferes with daily activities) to 4 (intolerable/always interferes with daily activities).¹⁶ Though widely used, the HDSS lacks a child-specific version and does not conform to current regulatory standards for PRO measures used to support product approvals and labeling. The DLQI/CDLQI are not hyperhidrosis-specific measures but are commonly used in dermatology clinical trials.¹⁷ These 10-item, skin disease-specific questionnaires assess how symptoms and treatment affect patient health-related quality of life. Higher scores on the 0-30 numeric rating scales indicate lower quality of life.

This post hoc analysis reports pooled pediatric (≥ 9 to ≤ 16 years) vs older subgroup (> 16 years) data at Week 4, including ASDD/ASDD-C Item 2 responder rate, mean and median absolute change from Baseline in gravimetrically measured sweat production, mean and median percent change from Baseline in sweat production, proportion of patients with $\geq 50\%$ reduction in sweat production, HDSS responder rate (≥ 2 -grade improvement from Baseline), and mean change from Baseline in DLQI and CDLQI. Data by week through Week 4 are also presented. Safety assessments included treatment-emergent adverse events (TEAEs) and local skin reactions (LSRs).

2.4 | Statistical analysis

Analysis subgroups were defined based on the DLQI and CDLQI, which have rigid age cutoffs for questionnaire administration (DLQI

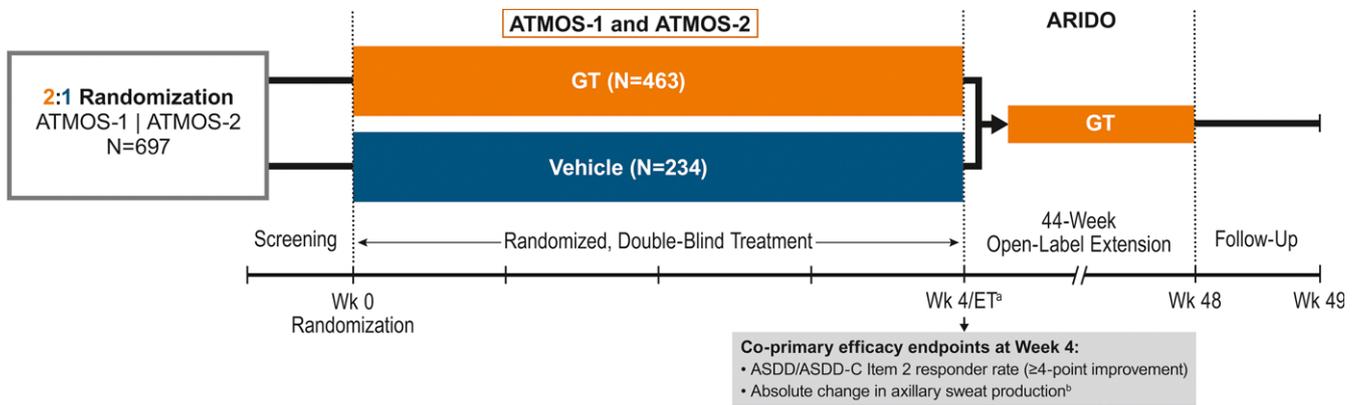


FIGURE 1 Study design

^aET for ATMOS-1 and ATMOS-2.

^bGravimetrically measured.

Patients not continuing in the open-label extension (ARIDO) had a safety follow-up at Week 5 via telephone.

ASDD, axillary sweating daily diary; ASDD-C, ASDD-Children; ET, end of treatment; GT, topical glycopyrronium tosylate; Wk, week

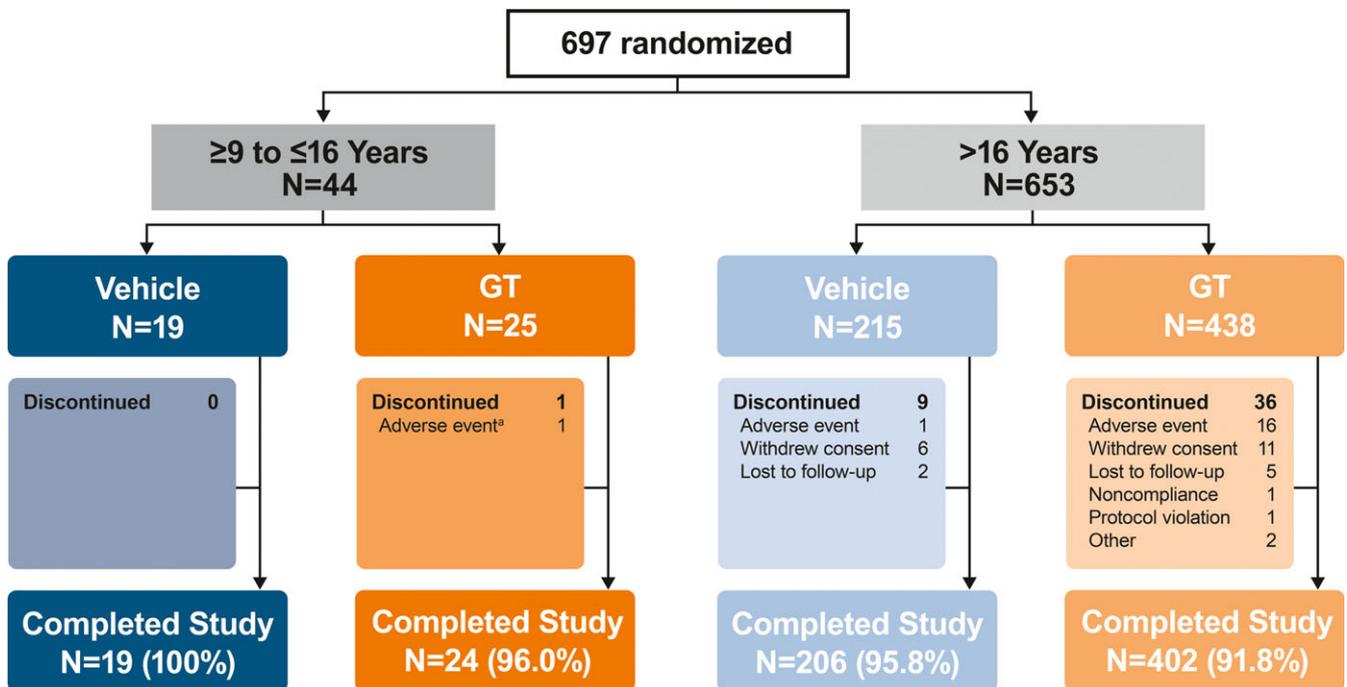


FIGURE 2 Patient disposition.

^aPatient had five drug-related events that led to discontinuation: mild vision blurred (bilateral), severe mydriasis (bilateral), severe dry mouth, severe urinary retention, and severe anhidrosis.

GT, topical glycopyrronium tosylate

was administered to those > 16 years while CDLQI was administered to those ≤ 16 years). Therefore, the pediatric subgroup included patients ≥ 9 to ≤ 16 years and the older subgroup included patients > 16 years. Since ASDD/ASDD-C Item 2 was psychometrically evaluated and validated, the standard age cutoffs (ASDD-C: < 6 years; ASDD: ≥ 16 years) for questionnaire administration could be and were modified to match the subgroup definitions established by the DLQI/CDLQI. All efficacy and safety assessments were made according to these subgroup definitions.

Efficacy analyses were conducted on the intent-to-treat population (all patients who were randomized and dispensed study drug). Markov chain Monte Carlo multiple imputation was used at Weeks 1-4. No imputation was made for DLQI/CDLQI. Analyses of statistical significance were not performed, as these comparisons were post hoc and not designed or powered to detect differences. Safety analyses were conducted on the safety population (all randomized patients who received ≥ 1 confirmed dose of study drug).

3 | RESULTS

3.1 | Patient disposition, demographics, and baseline disease characteristics

Of 697 patients randomized, 44 (GT, $n = 25$; vehicle, $n = 19$) comprised the pediatric subgroup (Figure 2). Completion rates were similar among subgroups and $> 90\%$. Demographics and Baseline disease characteristics were generally well matched among treatment arms and between subgroups (Table 1). Although the older subgroup had greater gravimetrically measured sweat production at Baseline, the standard deviations were large across all treatment groups.

3.2 | Efficacy

Efficacy results at Week 4 were consistent among subgroups and the overall pooled population.¹² ASDD/ASDD-C Item 2 responder rates were nearly identical among GT-treated patients in the

pediatric and older subgroups (59.9% vs 60.2%, respectively), and substantially greater for GT- vs vehicle-treated patients regardless of subgroup (Figure 3A). Differences in responder rates between GT and vehicle were observed as early as Week 1 and were maintained through Week 4 in both subgroups (Figure 3B).

Median change in gravimetrically measured sweat production is presented here given the small pediatric sample size and skewness of the data (ie, large standard deviations) (Table 2). GT-treated patients in the older subgroup had greater median absolute change from Baseline vs the pediatric subgroup (-80.6 vs -64.2 mg/5 minutes, respectively), and GT showed greater change vs vehicle in both subgroups. Mean percent change from Baseline in sweat production was similar among GT-treated patients in pediatric and older subgroups (-60.1% vs -56.2% , respectively), and greater for GT- vs vehicle-treated patients (Table 2). The proportion of patients with $\geq 50\%$ reduction in sweat production at Week 4 was similar between GT-treated pediatric and older patients (79.9% vs 74.3%; Table 2), with a markedly greater proportion of GT- vs vehicle-treated patients achieving this reduction. Differences between GT and

TABLE 1 Patient demographics and baseline disease characteristics

	≥ 9 to ≤ 16 y		> 16 y	
	Vehicle $n = 19$	GT $n = 25$	Vehicle $n = 215$	GT $n = 438$
Demographics				
Age (years)				
Mean (SD)	14.1 (1.7)	14.6 (1.4)	35.1 (11.2)	33.3 (10.5)
Median	14.0	15.0	33.0	32.0
Range	9-16	11-16	17-76	17-65
Sex, n (%)				
Male	4 (21.1)	5 (20.0)	110 (51.2)	207 (47.3)
Female	15 (78.9)	20 (80.0)	105 (48.8)	231 (52.7)
White, n (%)	17 (89.5)	18 (72.0)	179 (83.3)	356 (81.3)
Weight (kg)				
Mean (SD)	64.8 (15.8)	71.9 (15.7)	84.3 (19.0)	81.6 (19.3)
Median	62.6	72.3	83.0	79.8
Range	47.2-117.9	47.2-107.7	45.8-145.1	46.9-149.7
BMI (kg/m^2), mean (SD)	24.0 (5.2)	26.3 (5.6)	28.1 (5.1)	27.5 (5.4)
Baseline disease characteristics				
Years with axillary hyperhidrosis, mean (SD)	4.6 (3.6)	4.4 (4.1)	17.0 (10.5)	15.9 (10.8)
Sweat production (mg/5 min), ^a mean (SD)	151.7 (150.6)	145.8 (133.4)	178.4 (163.0)	174.0 (219.5)
ASDD/ASDD-C Item 2 (sweating severity), mean (SD)	6.7 (1.7)	7.5 (1.2)	7.2 (1.6)	7.3 (1.6)
HDSS, n (%)				
Grade 3	14 (73.7)	15 (60.0)	141 (65.6)	262 (59.8)
Grade 4	5 (26.3)	10 (40.0)	73 (34.0)	176 (40.2)
DLQI, ^b mean (SD)	NA ^c	NA ^c	10.6 (5.9)	11.9 (6.1)
CDLQI, mean (SD)	8.5 (5.6)	9.9 (5.5)	NA ^c	NA ^c

Intent-to-treat population.

ASDD, axillary sweating daily diary; ASDD-C, ASDD-Children; BMI, body mass index; CDLQI, children's DLQI; DLQI, dermatology life quality index; GT, topical glycopyrronium tosylate; HDSS, Hyperhidrosis Disease Severity Scale; NA, not applicable; SD, standard deviation.

^aGravimetrically measured average from the left and right axillae.

^b $n = 24$ for GT group ≥ 9 to ≤ 16 y of age.

^cPatients ≥ 9 to ≤ 16 y of age were administered the CDLQI and patients > 16 y of age were administered the DLQI.

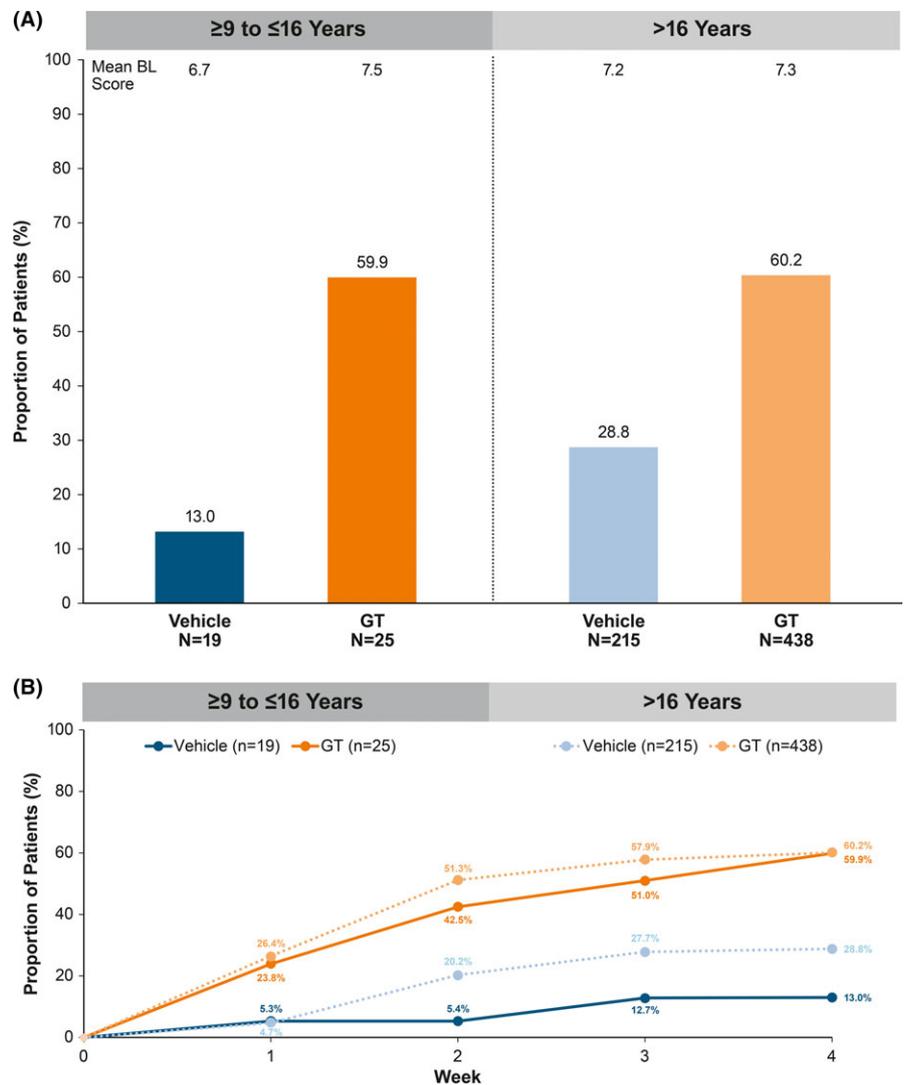


FIGURE 3 ASDD/ASDD-C Item 2 responder rate (≥ 4 -point improvement). A, At Week 4. B, To Week 4. Intent-to-treat population. *P*-values not calculated as these comparisons were post hoc and not designed or powered to detect differences. Multiple imputation (MCMC) was used to impute missing values for Weeks 1-4. ASDD, Axillary Sweating Daily Diary; ASDD-C, ASDD-Children; BL, baseline; GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

TABLE 2 Assessments of sweat production^a

	≥ 9 to ≤ 16 y		> 16 y	
	Vehicle n = 19	GT n = 25	Vehicle n = 215	GT n = 438
Absolute change from baseline at Week 4, mg/5 min				
Mean (SD)	-77.8 (110.6)	-67.9 (142.6)	-93.3 (141.9)	-109.9 (210.5)
Median	-53.7	-64.2	-62.0	-80.6
Percent change from Baseline at Week 4, mg/5 min				
Mean (SD)	-42.7 (38.2)	-60.1 (49.3)	-41.6 (47.9)	-56.2 (55.0)
Median	-55.3	-75.4	-54.1	-74.2
Proportion of patients with $\geq 50\%$ reduction at Week 4, %	54.8	79.9	53.0	74.3

Intent-to-treat population.

P-values not calculated as these comparisons were post hoc and not designed or powered to detect differences; multiple imputation (MCMC) was used to impute missing values.

GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo; SD, standard deviation.

^aGravimetrically measured.

vehicle were observed as early as Week 1 and were maintained through Week 4 for both subgroups (Figure 4).

HDSS responder rates were similar among GT-treated patients in the pediatric and older subgroups (61.3% vs 58.7%), and

approximately threefold greater for GT- vs vehicle-treated patients (Figure 5A) at Week 4. Differences between GT and vehicle were observed as early as Week 1 and were maintained through Week 4 for both subgroups (Figure 5B). Mean change from Baseline at

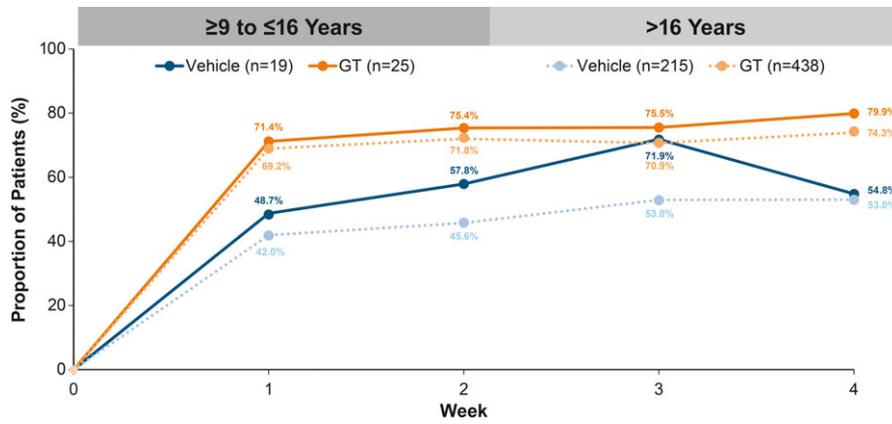


FIGURE 4 Proportion of patients with $\geq 50\%$ reduction in sweat production^a to Week 4.

^aGravimetrically measured average from the left and right axillae.

Intent-to-treat population.

P-values not calculated as these comparisons were post hoc and not designed or powered to detect differences.

Multiple imputation (MCMC) was used to impute missing values for Weeks 1-4. GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

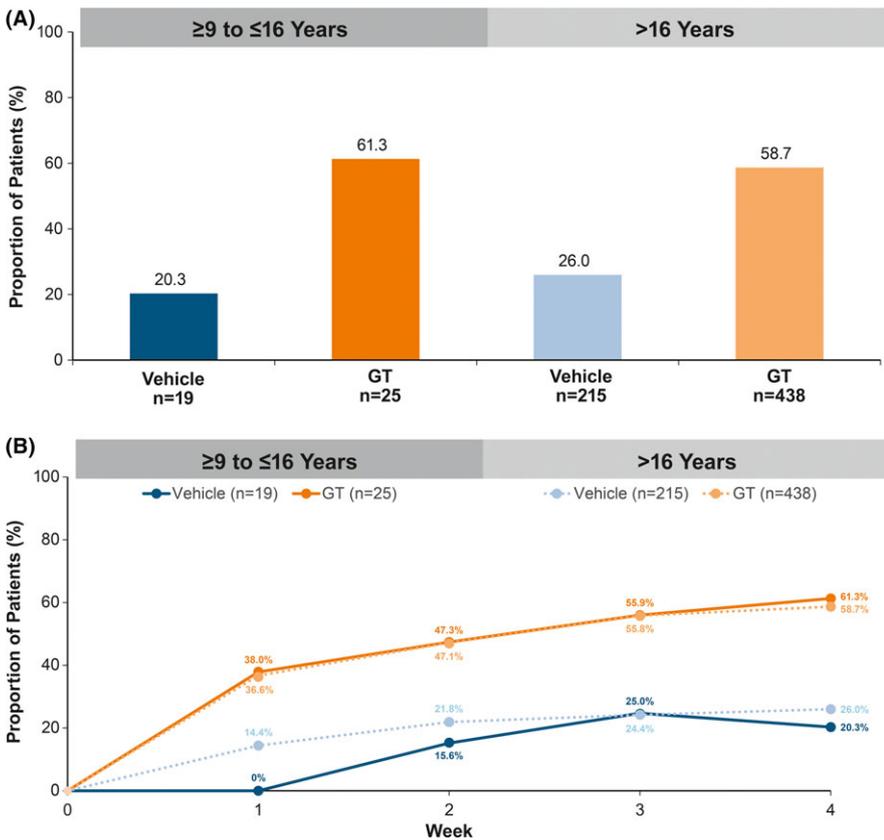


FIGURE 5 Hyperhidrosis Disease Severity Scale responder rate (≥ 2 -grade improvement). A, At Week 4. B, To Week 4. Intent-to-treat population. P-values not calculated as these comparisons were post hoc and not designed or powered to detect differences. Multiple imputation (MCMC) was used to impute missing values for Weeks 1-4. GT, topical glycopyrronium tosylate; MCMC, Markov chain Monte Carlo

Week 4 in CDLQI was consistent with that observed for DLQI in GT-treated patients in the pediatric and older subgroups (-8.1 vs -8.4; Figure 6). Mean decreases in CDLQI and DLQI scores observed for GT- vs vehicle-treated patients in each subgroup indicated a positive impact of GT treatment on health-related quality of life.

3.3 | Safety

Pediatric and older subgroups had similar safety profiles (Table 3). Slightly fewer pediatric patients reported TEAEs vs the older subgroup (Table 3). Of two serious TEAEs reported, both occurred in the GT arm of the older subgroup and only one led to

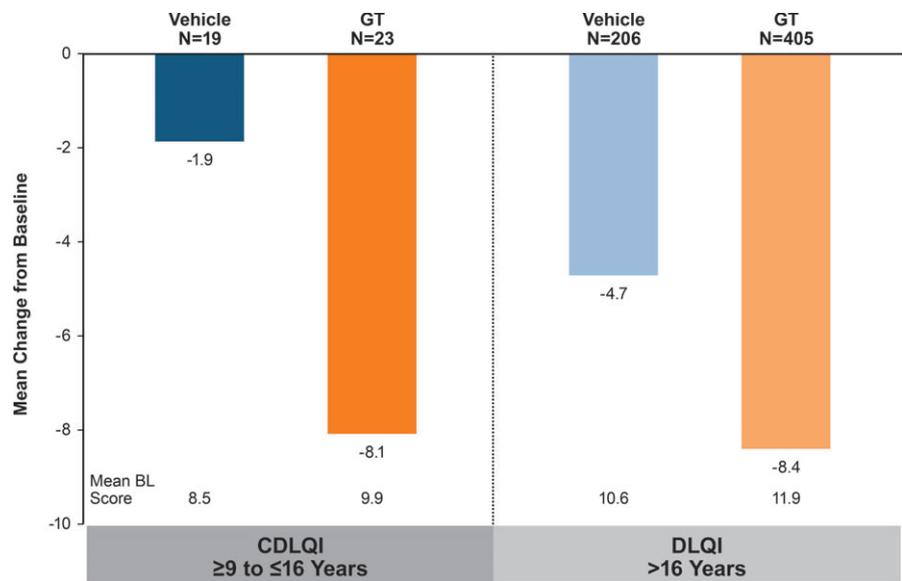


FIGURE 6 Mean change from Baseline at Week 4 in DLQI or CDLQI. Intent-to-treat population. *P*-values not calculated as these comparisons were post hoc and not designed or powered to detect differences. No imputation of missing values. BL, baseline; CDLQI, children's DLQI; DLQI, dermatology life quality index; GT, topical glycopyrronium tosylate

discontinuation (moderate unilateral mydriasis; related to treatment). The most frequently reported TEAEs with GT were related to anticholinergic activity and were mild, transient, and infrequently led to study discontinuation. Across subgroups, four patients experienced severe TEAEs; all events occurred in GT treatment groups and were considered related to treatment (pediatric subgroup: one patient with bilateral mydriasis, dry mouth, urinary retention, and anhidrosis [discontinued]; older subgroup: dry mouth [completed]; dry mouth [discontinued]; application site rash [completed]). A slightly greater proportion of GT-treated pediatric patients reported anticholinergic TEAEs vs GT-treated older subgroup patients (Table 3); the most frequently reported events were dry mouth and mydriasis in both subgroups. Of eight pediatric patients reporting anticholinergic TEAEs, most experienced ≥ 1 TEAE; all events were considered related to study treatment (Table 4). Most TEAEs in pediatric patients were mild, transient (resolving within approximately 2 weeks regardless of whether study drug was temporarily withheld), reversible, and were managed by temporarily withholding study treatment; TEAEs did not recur upon re-challenge. One pediatric patient discontinued (5 anticholinergic TEAEs, 4 of which were severe). Study drug was stopped on day of onset, and the TEAEs resolved within a week.

A similar proportion of patients across subgroups and treatment arms experienced LSRs (Table 5). Regardless of subgroup, the majority of GT- and vehicle-treated patients did not experience LSRs; of those that did, most were mild.

4 | DISCUSSION

This post hoc analysis is the first to report efficacy and safety data of topical, once-daily GT in pediatric patients with primary axillary hyperhidrosis. Though a limitation of the trial is the small sample size of the pediatric subgroup, the majority of the assessments showed consistent results between subgroups, and all assessments showed an advantage of GT treatment vs vehicle.

Although large variability was observed with sweat measurements, it is important to note that the episodic nature of sweating can complicate interpretation of gravimetrically measured sweat production.¹⁸ Despite this, both groups showed substantially reduced sweat production, and a greater proportion of GT- vs vehicle-treated patients were ASDD/ASDD-C Item 2 and HDSS responders, indicating that sweating severity decreased by Week 4. Despite limitations in gravimetrically measured sweat production, GT-treated patients, regardless of age, experienced meaningful reductions in sweating.

These subgroup data are consistent with previous findings of individual and pooled ATMOS-1 and ATMOS-2 data showing that GT improved disease symptoms, severity, and quality of life vs vehicle.^{12,19} ASDD/ASDD-C Item 2 responder rates were nearly identical among GT-treated pediatric and older subgroup patients. Pediatric patients also showed nearly identical responses to the older subgroup in HDSS responder rates and change from Baseline in DLQI/CDLQI. It should be noted that improvements were seen in both treatment arms across the efficacy measures evaluated within these trials. An effect of vehicle comparators has been observed in other dermatology trials,^{20,21} which underscore the choice to include a matching vehicle comparator in the ATMOS trials of GT to most accurately assess drug effect in these trials. The GT towelette contains the following excipients: citric acid, dehydrated alcohol, purified water, and sodium citrate.²² Identical excipients were included in the vehicle comparator of the ATMOS trials to account for any potential effect due to a compound other than active drug. Though a vehicle effect was observed in these trials, GT-treated patients had a significantly greater response than that observed with vehicle.^{12,19}

Glycopyrronium tosylate was generally well tolerated, and TEAEs in pediatric patients were qualitatively similar to those seen in the older subgroup and consistent with those expected with anticholinergics. Unlike mydriasis events in the older subgroup, which were largely unilateral (22 of 27 events), the majority in the pediatric

TABLE 3 Safety overview and TEAEs

n (%)	≥ 9 to ≤ 16 y		> 16 y	
	Vehicle n = 19	GT n = 25	Vehicle n = 213	GT n = 434
Any TEAE	2 (10.5)	11 (44.0)	73 (34.3)	246 (56.7)
Any serious TEAE	0	0	0	2 (0.5) ^a
Discontinuations due to TEAE	0	1 (4.0)	1 (0.5)	17 (3.9)
Deaths	0	0	0	0
TEAE by intensity				
Mild	2 (10.5)	6 (24.0)	51 (23.9)	164 (37.8)
Moderate	0	4 (16.0)	22 (10.3)	79 (18.2)
Severe	0	1 (4.0) ^b	0	3 (0.7) ^c
Anticholinergic TEAEs reported in > 2% of patients ^d				
Mydriasis	0	4 (16.0) ^e	0	27 (6.2) ^f
Vision blurred	0	3 (12.0)	0	13 (3.0)
Dry eye	0	1 (4.0)	1 (0.5)	10 (2.3)
Dry mouth	0	6 (24.0)	13 (6.1)	105 (24.2)
Urinary hesitation	0	0	0	16 (3.7)
Urinary retention	0	1 (4.0)	0	6 (1.4)
Nasal dryness	0	1 (4.0)	1 (0.5)	11 (2.5)
Constipation	0	0	0	9 (2.1)
Non-anticholinergic TEAEs reported in ≥ 5% of patients ^d				
Nausea	0	2 (8.0)	0	4 (0.9)
Application site pain	1 (5.3)	2 (8.0)	21 (9.9)	38 (8.8)
Pain	1 (5.3)	0	0	1 (0.2)
Influenza	1 (5.3)	0	2 (0.9)	3 (0.7)
Headache	0	1 (4.0)	5 (2.3)	22 (5.1)
Oropharyngeal pain	0	2 (8.0)	3 (1.4)	24 (5.5)
Epistaxis	0	2 (8.0)	1 (0.5)	3 (0.7)

Safety population.

Numbers in table represent number of patients reporting ≥ 1 TEAE and not number of events.

GT, topical glycopyrronium tosylate; TEAE, treatment-emergent adverse event.

^aModerate unilateral mydriasis considered by the Investigator to be related to treatment (discontinued); moderate dehydration considered unrelated to treatment (completed).

^bBilateral mydriasis, dry mouth, urinary retention, and anhidrosis (discontinued) considered related to treatment.

^cDry mouth (completed); dry mouth (discontinued); application site rash (completed); all events were considered related to treatment.

^dIn either treatment arm in either age subgroup in the pooled population.

^eOne patient reported a unilateral event; two patients reported bilateral events.

^fTwenty-two patients reported unilateral events; five patients reported bilateral events.

subgroup were bilateral (3 of 4 events). Although difficult to determine given the small number of events, this may be attributed to pediatric patients being more likely to touch both eyes after GT application or possibly anticholinergic effects resultant from systemic exposure, which are minimized but not eliminated completely by topical GT application. Even so, most patients completed the study. Overall, in both subgroups, most anticholinergic TEAEs were mild, transient, infrequently led to discontinuation, and did not recur with re-challenge. The majority of patients did not experience LSRs; most LSRs that were reported were mild in intensity.

A limitation of these studies is the relatively short duration compared to the chronic nature of primary hyperhidrosis. Results from the long-term open-label extension of these trials have been

reported, and safety findings from the pediatric subgroup are consistent with the results provided here from the double-blind trials.^{23,24}

Despite therapeutic options for axillary hyperhidrosis, patients generally remain dissatisfied with treatment.^{6,25} GT was FDA-approved in June 2018 for patients ≥ 9 years with primary axillary hyperhidrosis, representing the first approved treatment to include pediatric patients. For adults, this represents a second approved therapy in addition to onabotulinum toxinA,²⁶ a microwave device for sweat gland ablation²⁷ has also been cleared for use in adults. Oral anticholinergics are used off-label even though side effects remain a challenge. In a retrospective study of the oral anticholinergic glycopyrrolate in pediatric patients, the most highly cited

TABLE 4 Summary of anticholinergic TEAEs reported in GT-treated pediatric patients

Age/gender	Weight ^a (kg)	Study outcome	TEAE	Severity	Modification of dose	Resolution	Relationship to treatment
16/M	76.7	Completed	Dry mouth	Mild	No change	Resolved same day without treatment ^b	Related
16/F	74.4	Completed	Mydriasis (bilateral)	Moderate	Dose on day of onset skipped	Resolved 2 d later without treatment	Related ^c
16/F	86.2	Completed	Dry mouth	Mild	No change	Resolved 13 d later without treatment	Related
15/F	52.9	Completed	Vision blurred (bilateral)	Mild	Dose skipped 6 d after onset	Resolved 7 d later without treatment	Related
14/F	60.9	Completed	Dry mouth	Mild	No change	Continued untreated throughout study	Related
14/F	60.9	Completed	Mydriasis (bilateral)	Mild	Four doses skipped 6 d after onset	Resolved 8 d later without treatment	Related
14/F	60.9	Completed	Vision blurred (unilateral)	Moderate	Four doses skipped beginning on day of onset	Resolved 12 d later without treatment	Related
14/F	64.7	Completed	Mydriasis (unilateral)	Moderate		Resolved 15 d later without treatment	Related ^d
16/F	82.6	Completed	Dry eye	Mild	No change	Resolved same day without treatment	Related
16/F	82.6	Completed	Dry mouth	Mild	No change	Resolved 15 d later without treatment	Related
16/F	82.6	Completed	Dry mouth	Moderate	No change	Resolved 9 d later without treatment	Related
16/F	82.6	Completed	Nasal dryness	Mild	No change	Resolved 11 d later without treatment	Related
16/M	71.7	Discontinued	Vision blurred (bilateral)	Mild	Drug stopped on day of onset	Resolved 2 d later following treatment	Related
16/M	71.7	Discontinued	Mydriasis (bilateral)	Severe		Resolved 2 d later following treatment	Related
16/M	71.7	Discontinued	Dry mouth	Severe		Resolved 3 d later without treatment	Related
16/M	71.7	Discontinued	Urinary retention	Severe		Resolved 4 d later without treatment	Related
16/M	71.7	Discontinued	Anhidrosis	Severe		Resolved 6 d later without treatment	Related

d, day; F, female; GT, topical glycopyrronium tosylate; M, male; TEAE, treatment-emergent adverse event.

^aMeasured at screening.

^bPatient had six incidences of mild, treatment-related dry mouth. Five of six incidences resolved the same day without treatment; one of six resolved the following day without treatment.

^cBilateral mydriasis is a rare but reported occurrence in the setting of migraine headaches; the patient had a history of migraine and reported a moderate migraine at the time of mydriasis, which resolved at the same time as the TEAE.

^dDue to inadvertent direct exposure of GT to the eye.

TABLE 5 Summary of post-Baseline local skin reactions

n (%)	≥ 9 to ≤ 16 y		> 16 y	
	Vehicle n = 19	GT n = 25	Vehicle n = 212	GT n = 429
Any skin reaction	6 (31.6)	7 (28.0)	64 (30.2)	133 (31.0)
Burning/stinging	2 (10.5)	2 (8.0)	37 (17.5)	62 (14.5)
Dryness	0	1 (4.0)	3 (1.4)	15 (3.5)
Edema	0	0	6 (2.8)	13 (3.0)
Erythema	4 (21.1)	4 (16.0)	35 (16.5)	73 (17.0)
Pruritus	2 (10.5)	0	12 (5.7)	37 (8.6)
Scaling	0	1 (4.0)	3 (1.4)	12 (2.8)
Any LSR by maximum severity				
None	13 (68.4)	18 (72.0)	148 (69.8)	296 (69.0)
Mild	5 (26.3)	7 (28.0)	56 (26.4)	114 (26.6)
Moderate	1 (5.3)	0	6 (2.8)	18 (4.2)
Severe	0	0	2 (0.9)	1 (0.2)

Safety population.

A patient is counted as having a local skin reaction if any post-Baseline assessment is mild, moderate, or severe.

GT, topical glycopyrronium tosylate; LSR, local skin reaction.

reason for interrupting therapy was being bothered by side effects (62%).²⁸ Topical administration can reduce overall drug exposure and may mitigate adverse event risk.²⁹ Pharmacokinetic data show that maximum plasma concentration with topical GT once-daily for 5 days was low and comparable between children and adults ($C_{\max} = 0.07 \pm 0.06$ ng/mL in children age 10-17 years and $C_{\max} = 0.08 \pm 0.04$ ng/mL for adults).²² C_{\max} values for topical GT were lower than values reported in the literature for oral anticholinergics, though the potential for some systemic exposure with topical GT cannot be excluded.^{30,31}

A recent publication summarized favorable results on hyperhidrosis severity and quality of life in adolescents/young adults with topical administration of the anticholinergic oxybutynin, though this was a small (N = 10), uncontrolled pilot study.³² The unmet need for new therapies may be addressed with GT, which in this analysis mitigated disease severity while improving quality of life in pediatric patients, with a favorable safety profile. Additional trials that prospectively include pediatric patients with primary axillary hyperhidrosis are needed to confirm and expand the findings described here.

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CONFLICT OF INTEREST

Dr. Hebert is a consultant for Dermira, Inc., and an employee of the UTHealth McGovern Medical School, Houston, which received compensation from Dermira, Inc., for study participation. Dr. Glaser is a consultant for Dermira, Inc., and an investigator for Allergan;

Atacama Therapeutics; Brickell Biotech, Inc.; Galderma; and Revance Therapeutics, Inc. She has received honoraria for consulting with Allergan and Dermira, Inc. Dr. Green is an investigator for Brickell Biotech, Inc., and an advisory board member and investigator for Dermira, Inc. Dr. Werschler is a consultant and investigator for Dermira, Inc. Dr. Forsha is an investigator for Jordan Valley Dermatology and Research Center. Ms. Drew and Dr. Gopalan are employees of Dermira, Inc. Dr. Pariser received honoraria for consulting for Atacama Therapeutics; Brickell Biotech, Inc.; Biofrontera AG; Celgene Corporation; Dermira, Inc.; DUSA Pharmaceuticals, Inc.; LEO Pharma, Inc.; Novartis Pharmaceuticals Corporation; Promius Pharma; LLC; Regeneron Pharmaceuticals, Inc.; Sanofi; TDM SurgiTech, Inc.; TheraVida, Inc.; and Valeant Pharmaceuticals International, Inc. He received honoraria for advisory board participation for Pfizer, Inc. He received grants/research funding for serving as an investigator for Abbott Laboratories; Amgen, Inc.; Asana BioSciences; LLC; Brickell Biotech Inc.; Celgene Corporation; Dermavant Sciences, Inc.; Eli Lilly and Company; LEO Pharma, Inc.; Merck & Company, Inc.; Novartis Pharmaceuticals Corporation; Novo Nordisk A/S; Ortho Dermatologics, Inc.; Peplin, Inc.; Photocure ASA; Promius Pharma; LLC; Regeneron Pharmaceuticals, Inc.; Stiefel Laboratories; and Valeant Pharmaceuticals International, Inc. He received honoraria for serving as an investigator for LEO Pharma, Inc., and Pfizer, Inc.

STATEMENT OF APPROPRIATE IRB APPROVAL AND INFORMED CONSENT

The studies reported on herein were approved by institutional review boards.

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